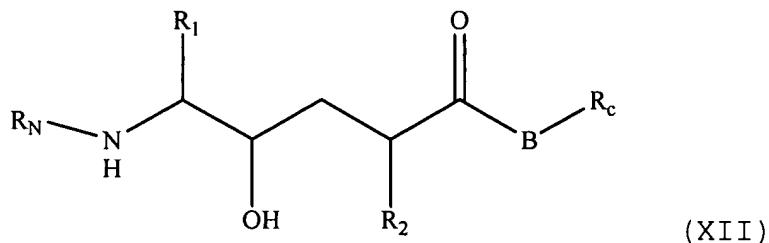


1-48. (Canceled)

49. (Currently Amended) A method for treating or preventing a disease characterized by beta-amyloid deposits in the brain comprising administering to a patient an effective therapeutic amount of a hydroxyethylene compound of the formula



where R<sub>1</sub> is:

- (I) C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted or substituted with one, two or three C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -NH<sub>2</sub>, -C≡N, -CF<sub>3</sub>, or -N<sub>3</sub>,
- (II) -(CH<sub>2</sub>)<sub>1-2</sub>-S-CH<sub>3</sub>,
- (III) -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>3</sub>,
- (IV) -CH<sub>2</sub>-(C<sub>2</sub>-C<sub>6</sub> alkenyl) unsubstituted or substituted by one -F,

(V) -(CH<sub>2</sub>)<sub>0-3</sub>-(R<sub>1</sub>-aryl) where R<sub>1</sub>-aryl is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

- (A) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (B) -CF<sub>3</sub>,
- (C) -F, Cl, -Br and -I,

(D) C<sub>1</sub>-C<sub>3</sub> alkoxy,

(E) -O-CF<sub>3</sub>,

(F) -NH<sub>2</sub>,

(G) -OH, or

(H) -C≡N,

(VI) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1</sub>-heteroaryl) where n<sub>1</sub> is 0, 1, 2, or 3 and

R<sub>1</sub>-heteroaryl is:

(A) pyridinyl,

(B) pyrimidinyl,

(C) quinolinyl,

(D) indenyl,

(E) indanyl,

(F) benzothiophenyl,

(G) indolyl,

(H) indolinyl,

(I) pyridazinyl,

(J) pyrazinyl,

(K) isoindolyl,

(L) isoquinolyl,

(M) quinazolinyl,

(N) quinoxalinyt,

(O) phthalazinyl,

(P) imidazolyl,

(Q) isoxazolyl,

(R) pyrazolyl,

(S) oxazolyl,

(T) thiazolyl,

(U) indolizinyl,

(V) indazolyl,

(W) benzothiazolyl,

(X) benzimidazolyl,

(Y) benzofuranyl,  
(Z) furanyl,  
(AA) thienyl,  
(BB) pyrrolyl,  
(CC) oxadiazolyl,  
(DD) thiadiazolyl,  
(EE) triazolyl,  
(FF) tetrazolyl,  
(GG) 1, 4-benzodioxan  
(HH) purinyl,  
(II) oxazolopyridinyl,  
(JJ) imidazopyridinyl,  
(KK) isothiazolyl,  
(LL) naphthyridinyl,  
(MM) cinnolinyl,  
(NN) carbazolyl,  
(OO)  $\beta$ -carbolinyl,  
(PP) isochromanyl,  
(QQ) chromanyl,  
(RR) furazanyl,  
(SS) tetrahydroisoquinoline,  
(TT) isoindolinyl,  
(UU) isobenzotetrahydrofuranyl,  
(VV) isobenzotetrahydrothienyl,  
(WW) isobenzothiophenyl,  
(XX) benzoxazolyl, or  
(YY) pyridopyridinyl,

where the R<sub>1</sub>-heteroaryl group is bonded to -(CH<sub>2</sub>)<sub>0-3</sub>- by any ring atom of the parent R<sub>N</sub>-heteroaryl group substituted by hydrogen such that the new bond to the R<sub>1</sub>-heteroaryl group replaces the hydrogen atom

and its bond, where heteroaryl is unsubstituted or substituted with one or two:

- (1) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (2) -CF<sub>3</sub>,
- (3) -F, Cl, -Br, or -I,
- (4) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (5) -O-CF<sub>3</sub>,
- (6) -NH<sub>2</sub>,
- (7) -OH, or
- (8) -C≡N,

with the proviso that when n<sub>1</sub> is zero R<sub>1</sub>-heteroaryl is not bonded to the carbon chain by nitrogen, or

(VII) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1</sub>-heterocycle) where n<sub>1</sub> is as defined above and

R<sub>1</sub>-heterocycle is:

- (A) morpholinyl,
- (B) thiomorpholinyl,
- (C) thiomorpholinyl S-oxide,
- (D) thiomorpholinyl S,S-dioxide,
- (E) piperazinyl,
- (F) homopiperazinyl,
- (G) pyrrolidinyl,
- (H) pyrrolinyl,
- (I) tetrahydropyrananyl,
- (J) piperidinyl,
- (K) tetrahydrofurananyl, or
- (L) tetrahydrothiophenyl,

where the R<sub>1</sub>-heterocycle group is bonded by any atom of the parent R<sub>1</sub>-heterocycle group substituted by hydrogen such that the new bond to the R<sub>1</sub>-heteroaryl group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or

two:

- (1) =O,
- (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (3) -CF<sub>3</sub>,
- (4) -F, Cl, -Br and -I,
- (5) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (6) -O-CF<sub>3</sub>,
- (7) -NH<sub>2</sub>,
- (8) -OH, or
- (9) -C≡N,

with the proviso that when n<sub>1</sub> is zero R<sub>1</sub>-heterocycle is not bonded to the carbon chain by nitrogen;

where R<sub>2</sub> is:

- (I) -H,
- (II) C<sub>1</sub>-C<sub>6</sub> alkyl, or
- (III) -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>2-1</sub> where R<sub>2-1</sub> is (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, R<sub>1</sub>-aryl or R<sub>1</sub>-heteroaryl where R<sub>1</sub>-aryl and R<sub>1</sub>-heteroaryl are as defined above,

where R<sub>N</sub> is:

- (I) R<sub>N-1</sub>-X<sub>N</sub>- where X<sub>N</sub> is:
  - (A) -CO-,
  - (B) -SO<sub>2</sub>-,
  - (C) -(CR'R'')<sub>1-6</sub> where R' and R'' are the same or different and are -H or C<sub>1</sub>-C<sub>4</sub> alkyl,
  - (D) -CO-(CR'R'')<sub>1-6</sub>-X<sub>N-1</sub> where X<sub>N-1</sub> is -O-, -S- and -NR'R''- and where R' and R'' are as defined above,
  - (E) a single bond;

where R<sub>N-1</sub> is:

- (A) R<sub>N</sub>-aryl where R<sub>N</sub>-aryl is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with

one, two, three or four of the following substituents which can be the same or different and are:

- (1)  $C_1-C_6$  alkyl,
- (2) -F, -Cl, -Br, or -I,
- (3) -OH,
- (4)  $-NO_2$ ,
- (5)  $-CO-OH$ ,
- (6)  $-C\equiv N$ ,
- (7)  $-CO-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are:

- (a) -H,
- (b)  $-C_1-C_6$  alkyl unsubstituted or substituted with one
  - (i) -OH, or
  - (ii)  $-NH_2$ ,
- (c)  $-C_1-C_6$  alkyl unsubstituted or substituted with one to three -F, -Cl, -Br, or -I,
- (d)  $-C_3-C_7$  cycloalkyl,
- (e)  $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl})$ ,
- (f)  $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$ ,
- (g)  $-C_1-C_6$  alkenyl with one or two

double bonds,

- (h)  $-C_1-C_6$  alkynyl with one or two triple bonds,
  - (i)  $-C_1-C_6$  alkyl chain with one double bond and one triple bond,
  - (j)  $-R_{1-\text{aryl}}$  where  $R_{1-\text{aryl}}$  is as defined above, or

(k) -R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl is as defined above,

- (8) -CO-(C<sub>3</sub>-C<sub>12</sub> alkyl),
- (9) -CO-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl),
- (10) -CO-R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl is as defined above,

(11) -CO-R<sub>1</sub>-heterocycle where R<sub>1</sub>-heterocycle is as defined above,

- (12) -CO-R<sub>N-4</sub> where R<sub>N-4</sub> is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C<sub>1</sub>-C<sub>3</sub> alkyl,

(13) -CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is:

- (a) C<sub>1</sub>-C<sub>6</sub> alkyl, or
- (b) -(CH<sub>2</sub>)<sub>0-2</sub>-(R<sub>1</sub>-aryl) where R<sub>1</sub>-aryl is as defined above,

(14) -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,

(15) -SO-(C<sub>1</sub>-C<sub>8</sub> alkyl),

(16) -SO<sub>2</sub>-(C<sub>3</sub>-C<sub>12</sub> alkyl),

(17) -NH-CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(18) -NH-CO-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(19) -N-CS-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(20) -N(C<sub>1</sub>-C<sub>3</sub> alkyl)-CO-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(21) -NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> can be the same or different and are as defined above,

(22) -R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,

- (23) -O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),
- (24) -O-CO-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,
- (25) -O-CS-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,
- (26) -O-(C<sub>1</sub>-C<sub>6</sub> alkyl),
- (27) -O-(C<sub>2</sub>-C<sub>5</sub> alkyl)-COOH,
- (28) -S-(C<sub>1</sub>-C<sub>6</sub> alkyl),
- (29) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 -F,
- (30) -O-(C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 -F, or
- (31) -O-Φ,

(B) -R<sub>N</sub>-heteroaryl where R<sub>N</sub>-heteroaryl is:

- (A) pyridinyl,
- (B) pyrimidinyl,
- (C) quinolinyl,
- (D) indenyl,
- (E) indanyl,
- (F) benzothiophenyl,
- (G) indolyl,
- (H) indolinyl,
- (I) pyridazinyl,
- (J) pyrazinyl,
- (K) isoindolyl,
- (L) isoquinolyl,
- (M) quinazolinyl,
- (N) quinoxalinyl,
- (O) phthalazinyl,
- (P) imidazolyl,
- (Q) isoxazolyl,
- (R) pyrazolyl,
- (S) oxazolyl,

(T) thiazolyl,  
(U) indolizinyl,  
(V) indazolyl,  
(W) benzothiazolyl,  
(X) benzimidazolyl,  
(Y) benzofuranyl,  
(Z) furanyl,  
(AA) thietyl,  
(BB) pyrrolyl,  
(CC) oxadiazolyl,  
(DD) thiadiazolyl,  
(EE) triazolyl,  
(FF) tetrazolyl,  
(GG) 1, 4-benzodioxan  
(HH) purinyl,  
(II) oxazolopyridinyl,  
(JJ) imidazopyridinyl,  
(KK) isothiazolyl,  
(LL) naphthyridinyl,  
(MM) cinnolinyl,  
(NN) carbazolyl,  
(OO)  $\beta$ -carbolinyl,  
(PP) isochromanyl,  
(QQ) chromanyl,  
(RR) furazanyl,  
(SS) tetrahydroisoquinoline,  
(TT) isoindolinyl,  
(UU) isobenzotetrahydrofuranyl,  
(VV) isobenzotetrahydrothienyl,  
(WW) isobenzothiophenyl,  
(XX) benzoxazolyl, or

(YY) pyridopyridinyl,

where the R<sub>N</sub>-heteroaryl group is bonded by any atom of the parent R<sub>N</sub>-heteroaryl group substituted by hydrogen such that the new bond to the R<sub>N</sub>-heteroaryl group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

- (1) C<sub>1</sub>-C<sub>6</sub> alkyl,
- (2) -F, -Cl, -Br, or -I,
- (3) -OH,
- (4) -NO<sub>2</sub>,
- (5) -CO-OH,
- (6) -C≡N,
- (7) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are the same or different and are:

- (a) -H,
- (b) -C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with one
  - (i) -OH, or
  - (ii) -NH<sub>2</sub>,
- (c) -C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1, 2, or 3 -F, -Cl, -Br, or -I,
- (d) -C<sub>3</sub>-C<sub>7</sub> cycloalkyl,
- (e) -(C<sub>1</sub>-C<sub>2</sub> alkyl)-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl),
- (f) -(C<sub>1</sub>-C<sub>6</sub> alkyl)-O-(C<sub>1</sub>-C<sub>3</sub> alkyl),
- (g) -C<sub>1</sub>-C<sub>6</sub> alkenyl with one or two double bonds,
- (h) -C<sub>1</sub>-C<sub>6</sub> alkynyl with one or two triple bonds,

- (i) -C<sub>1</sub>-C<sub>6</sub> alkyl chain with one double bond and one triple bond,
- (j) -R<sub>1</sub>-aryl where R<sub>1</sub>-aryl is as defined above, or
- (k) -R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl is as defined above,

(8) -CO-(C<sub>3</sub>-C<sub>12</sub> alkyl),

(9) -CO-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl),

(10) -CO-R<sub>1</sub>-heteroaryl where R<sub>1</sub>-heteroaryl is as defined above,

(11) -CO-R<sub>1</sub>-heterocycle where R<sub>1</sub>-heterocycle is as defined above,

(12) -CO-R<sub>N-4</sub> where R<sub>N-4</sub> is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two C<sub>1</sub>-C<sub>3</sub> alkyl,

(13) -CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is:

- (a) C<sub>1</sub>-C<sub>6</sub> alkyl, or
- (b) -(CH<sub>2</sub>)<sub>0-2-</sub>(R<sub>1</sub>-aryl) where R<sub>1</sub>-aryl is as defined above,

(14) -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,

(15) -SO-(C<sub>1</sub>-C<sub>8</sub> alkyl),

(16) -SO<sub>2</sub>-(C<sub>3</sub>-C<sub>12</sub> alkyl),

(17) -NH-CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(18) -NH-CO-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(19) -N-CS-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(20)  $-N(C_1-C_3\text{ alkyl})-CO-R_{N-5}$  where  $R_{N-5}$  is as defined above,

(21)  $-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  can be the same or different and are as defined above,

(22)  $-R_{N-4}$  where  $R_{N-4}$  is as defined above,

(23)  $-O-CO-(C_1-C_6\text{ alkyl}),$

(24)  $-O-CO-N(C_1-C_3\text{ alkyl})_2,$

(25)  $-O-CS-N(C_1-C_3\text{ alkyl})_2,$

(26)  $-O-(C_1-C_6\text{ alkyl}),$

(27)  $-O-(C_2-C_5\text{ alkyl})-COOH,$  or

(28)  $-S-(C_1-C_6\text{ alkyl}),$

(C)  $-R_{N-aryl}-R_{N-aryl}$  where  $-R_{N-aryl}$  is as defined above,

(D)  $-R_{N-aryl}-R_{N-heteroaryl}$  where  $-R_{N-aryl}$  and  $-R_{N-heteroaryl}$  are as defined above,

(E)  $-R_{N-heteroaryl}-R_{N-aryl}$  where  $-R_{N-aryl}$  and  $-R_{N-heteroaryl}$  are as defined above,

(F)  $-R_{N-heteroaryl}-R_{N-heteroaryl}$  where  $R_{N-heteroaryl}$  is as defined above,

(G)  $-R_{N-aryl}-O-R_{N-aryl}$  where  $-R_{N-aryl}$  is as defined above,

(H)  $-R_{N-aryl}-S-R_{N-aryl}$  where  $-R_{N-aryl}$  is as defined above,

(I)  $-R_{N-heteroaryl}-O-R_{N-heteroaryl}$  where  $R_{N-heteroaryl}$  is as defined above,

(J)  $-R_{N-heteroaryl}-S-R_{N-heteroaryl}$  where  $R_{N-heteroaryl}$  is as defined above,

(K)  $-R_{N-aryl}-CO-R_{N-aryl}$  where  $-R_{N-aryl}$  is as defined above,

(L)  $-R_N\text{-aryl}-CO-R_N\text{-heteroaryl}$  where  $R_N\text{-aryl}$  and  $R_N\text{-heteroaryl}$  are as defined above,

(M)  $-R_N\text{-aryl}-SO_2-R_N\text{-aryl}$  where  $R_N\text{-aryl}$  is as defined above,

(N)  $-R_N\text{-heteroaryl}-CO-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(O)  $-R_N\text{-heteroaryl}-SO_2-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(P)  $-R_N\text{-aryl}-O-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-aryl}$  is as defined above,

(Q)  $-R_N\text{-aryl}-S-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-aryl}$  is as defined above,

(R)  $-R_N\text{-heteroaryl}-O-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-heteroaryl}$  is as defined above, or

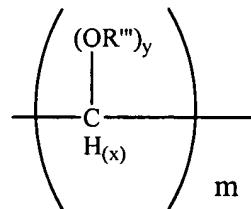
(S)  $-R_N\text{-heteroaryl}-S-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-heteroaryl}$  is as defined above,

(II)  $A-X_N-$  where  $X_N$  is  $-CO-$ ,

wherein A is

(A)  $-T-E-(Q)_m$ ,

(1) where -T is



where

(a)  $x = 1$  when  $y = 1$  and  $x = 2$  when  $y = 0$ ,

(b)  $m$  is  $0, 1, 2$  or  $3$ ,

- (c) the values of x and y vary independently on each carbon when m is 2 and 3, and
- (d) R''' varies independently on each carbon and is H, (C<sub>1</sub>-C<sub>2</sub>) alkyl, phenyl, or phenyl(C<sub>1</sub>-C<sub>3</sub>)alkyl;

(2) -E is

(a) C<sub>1</sub>-C<sub>5</sub> alkyl, but only if m' does not equal 0,

- (b) methylthioxy(C<sub>2</sub>-C<sub>4</sub>)alkyl,
- (c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,

(e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,

(f) biphenyl,

(g) diphenyl ether,

(h) diphenylketone,

(i) phenyl(C<sub>1</sub>-C<sub>8</sub>)alkyloxyphenyl, or

(j) C<sub>1</sub>-C<sub>6</sub> alkoxy;

(3) -Q is

- (a) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (b) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (c) C<sub>1</sub>-C<sub>3</sub> alkylthioxy,
- (d) C<sub>1</sub>-C<sub>6</sub> alkylacylamino,
- (e) C<sub>1</sub>-C<sub>6</sub> alkylacyloxy,

(f) amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary amino moieties),  
(g) C<sub>1</sub>-C<sub>6</sub> alkylamino  
(h) phenylamino,  
(i) carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters),  
(j) carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters),  
(k) carboxy(C<sub>2</sub>-C<sub>5</sub>)alkoxy,  
(l) carboxy(C<sub>2</sub>-C<sub>5</sub>)alkylthioxy,  
(m) heterocyclacyl,  
(n) heteroarylacyl, or  
(o) hydroxyl;  
(4) m' is 0, 1, 2 or 3;  
  
(B) -E(Q)<sub>m''</sub> wherein E and -Q are as defined as above and m'' is 0, 1, 2, or 3;  
(C) -T-E wherein -E and -Q are as defined as above; or  
(D) -E wherein -E is as defined as above;  
  
(III) -CO-(C<sub>1</sub>-C<sub>6</sub> alkyl) where alkyl is unsubstituted or substituted with one or two:  
(A) -OH,  
(B) -C<sub>1</sub>-C<sub>6</sub> alkoxy,  
(C) -C<sub>1</sub>-C<sub>6</sub> thioalkoxy,  
(D) -CO-O-R<sub>N-8</sub> where R<sub>N-8</sub> is -H, C<sub>1</sub>-C<sub>6</sub> alkyl or -Φ,  
(E) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are the same or different and are as defined above,  
(F) -CO-R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,  
(G) -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkyl),

(H)  $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  where  $\text{R}_{\text{N}-2}$  and  $\text{R}_{\text{N}-3}$  are the same or different and are as defined above,

(I)  $-\text{NH}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$

(J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$  where  $\text{R}_{\text{N}-8}$  is as defined above,

(K)  $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  where  $\text{R}_{\text{N}-2}$  and  $\text{R}_{\text{N}-3}$  are the same or different and are as defined above,

(L)  $-\text{R}_{\text{N}-4}$  where  $\text{R}_{\text{N}-4}$  is as defined above,

(M)  $-\text{O}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$

(N)  $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$  where the  $\text{R}_{\text{N}-8}$  is the same or different and are as defined above, or

(O)  $-\text{O}- (\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH},$

(IV)  $-\text{CO}- (\text{C}_1-\text{C}_3 \text{ alkyl})-\text{O}- (\text{C}_1-\text{C}_3 \text{ alkyl})$  where alkyl is unsubstituted or substituted with one or two

(A)  $-\text{OH},$

(B)  $-\text{C}_1-\text{C}_6 \text{ alkoxy},$

(C)  $-\text{C}_1-\text{C}_6 \text{ thioalkoxy},$

(D)  $-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$  where  $\text{R}_{\text{N}-8}$  is  $-\text{H}$ ,  $\text{C}_1-\text{C}_6$  alkyl or  $-\phi,$

(E)  $-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  where  $\text{R}_{\text{N}-2}$  and  $\text{R}_{\text{N}-3}$  are the same or different and are as defined above,

(F)  $-\text{CO}-\text{R}_{\text{N}-4}$  where  $\text{R}_{\text{N}-4}$  is as defined above,

(G)  $-\text{SO}_2- (\text{C}_1-\text{C}_8 \text{ alkyl}),$

(H)  $-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  where  $\text{R}_{\text{N}-2}$  and  $\text{R}_{\text{N}-3}$  are the same or different and are as defined above,

(I)  $-\text{NH}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$

(J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$  where  $\text{R}_{\text{N}-8}$  is as defined above,

(K)  $-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$  where  $\text{R}_{\text{N}-2}$  and  $\text{R}_{\text{N}-3}$  are the same or different and are as defined above,

(L)  $-\text{R}_{\text{N}-4}$  where  $\text{R}_{\text{N}-4}$  is as defined above,

(M)  $-\text{O}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$

(N)  $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$  where the  $\text{R}_{\text{N}-8}$  are the same or different and are as defined above, or

(O)  $-O-(C_1-C_5 \text{ alkyl})-COOH$ ,

(V)  $-CO-(C_1-C_3 \text{ alkyl})-S-(C_1-C_3 \text{ alkyl})$  where alkyl is unsubstituted or substituted with one or two

(A)  $-OH$ ,

(B)  $-C_1-C_6 \text{ alkoxy}$ ,

(C)  $-C_1-C_6 \text{ thioalkoxy}$ ,

(D)  $-CO-O-R_{N-8}$  where  $R_{N-8}$  is  $-H$ ,  $C_1-C_6$  alkyl or  $-\phi$ ,

(E)  $-CO-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,

(F)  $-CO-R_{N-4}$  where  $R_{N-4}$  is as defined above,

(G)  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,

(H)  $-SO_2-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,

(I)  $-NH-CO-(C_1-C_6 \text{ alkyl})$ ,

(J)  $-NH-CO-O-R_{N-8}$  where  $R_{N-8}$  is as defined above,

(K)  $-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,

(L)  $-R_{N-4}$  where  $R_{N-4}$  is as defined above,

(M)  $-O-CO-(C_1-C_6 \text{ alkyl})$ ,

(N)  $-O-CO-NR_{N-8}R_{N-8}$  where the  $R_{N-8}$  are the same or different and are as defined above, or

(O)  $-O-(C_1-C_5 \text{ alkyl})-COOH$ ,

(VI)  $-CO-CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-R_{N-aryl}/R_{N-heteroaryl}$  where  $R_{N-aryl}$  and  $R_{N-heteroaryl}$  are as defined above, where  $R_{N-10}$  is:

(A)  $-H$ ,

(B)  $C_1-C_6 \text{ alkyl}$ ,

(C)  $C_3-C_7 \text{ cycloalkyl}$ ,

(D)  $C_2-C_6 \text{ alkenyl}$  with one double bond,

(E)  $C_2-C_6 \text{ alkynyl}$  with one triple bond,

(F)  $R_1\text{-aryl}$  where  $R_1\text{-aryl}$  is as defined above, or

(G)  $R_N$ -heteroaryl where  $R_N$ -heteroaryl is as defined above;

where B is -O-, -NH-, or -N( $C_1$ - $C_6$  alkyl)-;

where  $R_C$  is:

(I)  $(C_1-C_{10})$  alkyl  $K_{1-3}$ , in which:

\_\_\_\_\_ (A) the alkyl chain is unsubstituted or substituted with one -OH,

\_\_\_\_\_ (B) the alkyl chain is unsubstituted or

substituted with one  $C_1-C_6$  alkoxy unsubstituted or substituted with 1-5 F,

\_\_\_\_\_ (C) the alkyl chain is unsubstituted or substituted with one -O- $\phi$ ,

\_\_\_\_\_ (D) the alkyl chain is unsubstituted or substituted with 1-5 F,

\_\_\_\_\_ (E) the alkyl chain is unsubstituted or substituted with a combination of up to three atoms of oxygen and sulfur each such atom replacing one carbon,

\_\_\_\_\_ (F) each K is:

\_\_\_\_\_ (1) H,

\_\_\_\_\_ (2)  $C_1-C_3$  alkyl,

\_\_\_\_\_ (3)  $C_1-C_3$  alkoxy,

\_\_\_\_\_ (4)  $C_1-C_3$  alkylthioxy,

\_\_\_\_\_ (5)  $C_1-C_6$  alkylacylamine,

\_\_\_\_\_ (6)  $C_1-C_6$  alkylacylexy,

\_\_\_\_\_ (7) amide

\_\_\_\_\_ (8)  $C_1-C_6$  alkylamine

\_\_\_\_\_ (9) phenylamine,

\_\_\_\_\_ (10) carbamyl

\_\_\_\_\_ (11) carboxyl

(12) carboxy ( $C_2-C_5$ ) alkoxy,  
(13) carboxy ( $C_2-C_5$ ) alkylthioxy,  
(14) heterocyclacylacyl,  
(15) heteroarylacyl,  
(16) amino unsubstituted or substituted  
with  $C_1-C_6$  alkyl,  
(17) hydroxyl, or  
(18) carboxyl methyl ester;

(II)  $-(CH_2)_{0-3}-J-\{-(CH_2)_{0-3}-K\}_{1-3}$ , where K is as defined  
above and J is:

(A) a 5 to 7 atom monocyclic aryl group,  
(B) a 8 to 12 atom multicyclic aryl group,  
(C) a 5 to 7 atom heterocyclic group,  
(D) a 8 to 12 atom multicyclic heterocyclic  
group, or  
(E) a 5 to 10 atom monocyclic or multicyclic  
cycloalkyl group;

(III)  $-(CH_2)_{0-3}-(C_3-C_7)$  cycloalkyl where cycloalkyl can  
be unsubstituted or substituted with one, two or  
three

(A)  $C_1-C_3$  alkyl unsubstituted or substituted with  
1, 2, 3, or 4 -F,

-Cl, -Br, or -I,

(B) -CO-OH,  
(C) -CO-O- ( $C_1-C_4$  alkyl),  
(D) -OH, or  
(E)  $C_1-C_6$  alkoxy,

(IV)  $-(CH_2)_{2-6}-OH$ ,

(V)  $-(CR_{C_x}R_{C_y})_{0-4}-R_{C Aryl}$  where  $R_{C_x}$  and  $R_{C_y}$  are H,  $C_1-C_4$   
alkyl and  $\phi$  and  $R_{C Aryl}$  is the same as  $R_{N Aryl}$ ,

(VI)  $(CH_2)_{0-4}-R_c$  heteraryl where  $R_c$  heteraryl is:

- (A) pyridinyl,
- (B) pyrimidinyl,
- (C) quinolinyl,
- (D) indenyl,
- (E) indanyl,
- (F) benzothiophenyl,
- (G) indolyl,
- (H) indolinyl,
- (I) pyridazinyl,
- (J) pyrazinyl,
- (K) isoindolyl,
- (L) isoquinolyl,
- (M) quinazolinyl,
- (N) quinoxalinyl,
- (O) phthalazinyl,
- (P) isoxazolyl,
- (Q) pyrazolyl,
- (R) indolizinyl,
- (S) indazolyl,
- (T) benzothiazolyl,
- (U) benzimidazolyl,
- (V) benzofuranyl,
- (W) furanyl,
- (X) thienyl,
- (Y) pyrrolyl,
- (Z) oxadiazolyl,
- (AA) thiadiazolyl,
- (BB) triazolyl,
- (CC) tetrazolyl,
- (DD) 1, 4-benzodioxan

(EE) purinyl,  
 (FF) oxazolopyridinyl,  
 (GG) imidazopyridinyl,  
 (HH) isothiazolyl,  
 (II) naphthyridinyl,  
 (JJ) cinnolinyl,  
 (KK) carbazolyl,  
 (LL)  $\beta$ -carbolinyl,  
 (MM) iso chromanyl,  
 (NN) chromanyl,  
 (OO) furazanyl,  
 (PP) tetrahydroisoquinoline,  
 (QQ) isoindolinyl,  
 (RR) iso benzotetrahydrofuranyl,  
 (SS) iso benzotetrahydrothienyl,  
 (TT) iso benzothiophenyl,  
 (UU) benzoxazolyl, or  
 (VV) pyridopyridinyl,  
 (VII)  $-(CH_2)_0-4-R_C-heterocycle$  where  $R_C-heterocycle$  is the same as  $R_1-heterocycle$ ,  
 (VIII)  $-C(R_{C-1})(R_{C-2})CO-NH-R_{C-3}$  where  $R_{C-1}$  and  $R_{C-2}$  are the same or different and are:  
 (A) H,  
 (B)  $C_1-C_6$  alkyl,  
 (C)  $-(C_1-C_4$  alkyl)  $-R_{C'-aryl}$  where  $R_{C'-aryl}$  is as defined above for  
 $R_1-aryl$   
 (D)  $-(C_1-C_4$  alkyl)  $-R_C-heteroaryl$  where  $R_C-heteroaryl$  is as defined above,  
 (E)  $-(C_1-C_4$  alkyl)  $-R_C-heterocycle$  where  $R_C-heterocycle$  is as defined above,

(F)  $-R_C-heteroaryl$  where  $R_C-heteroaryl$  is as defined above,

(G)  $-R_C-heterocycle$  where  $R_C-heterocycle$  is as defined above,

(H)  $-(CH_2)_{1-4}-OH$ ,

(I)  $-(CH_2)_{1-4}-R_C-4-(CH_2)_{1-4}-R_C'-aryl$  where  $R_C-4$  is  $O$ ,  $S$ ,  $NH$  or  
 $-NHR_C-5$  where  $R_C-5$  is  $C_1-C_6$  alkyl, and where  $R_C'-aryl$  is as defined above,

(J)  $-(CH_2)_{1-4}-R_C-4-(CH_2)_{1-4}-R_C-heteroaryl$  where  $R_C-4$  and  $R_C-heteroaryl$  are as defined above, or

(K)  $-R_C'-aryl$  where  $R_C'-aryl$  is as defined above, and where  $R_C-3$  is:

(A)  $H$ ,

(B)  $C_1-C_6$  alkyl,

(C)  $-R_C'-aryl$  where  $R_C'-aryl$  is as defined above,

(D)  $-R_C-heteroaryl$  where  $R_C-heteroaryl$  is as defined above,

(E)  $-R_C-heterocycle$  where  $R_C-heterocycle$  is as defined above,

(F)  $-(C_1-C_4\text{ alkyl})-R_C'-aryl$  where  $R_C'-aryl$  is as defined above,

(G)  $-(C_1-C_4\text{ alkyl})-R_C-heteroaryl$  where  $R_C-heteroaryl$  is as defined above, or

(H)  $-(C_1-C_4\text{ alkyl})-R_C-heterocycle$  where  $R_C-heterocycle$  is as defined above,

(IX)  $CH(\Phi)_{27}$

(X) cyclopentyl or cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one, two or three:

(A)  $C_1-C_3$ -alkyl,  
(B)  $-CF_3$ ,  
(C) -F, Cl, Br and I,  
(D)  $C_1-C_3$ -alkoxy,  
(E)  $-OCF_3$ ,  
(F)  $-NH_2$ ,  
(G) -OH, or  
(H)  $-C\equiv N$ ,  
(XI)  $CH_2-C\equiv CH$ ;  
(XII)  $-(CH_2)_{0-1}-CHR_{e-5}-(CH_2)_{0-1}-\phi$  where  $R_{e-5}$  is:  
(A) -OH, or  
(B)  $CH_2-OH$ ;  
(XIII)  $CH(\phi)-CO-O(C_1-C_3\text{-alkyl})$ ;  
(XIV)  $CH(CH_2-OH)-CH(OH)-\phi-NO_2$ ;  
(XV)  $(CH_2)_2-O-(CH_2)_2-OH$ ;  
(XVI)  $CH_2-NH-CH_2-CH(O-CH_2-CH_3)_2$ ;  
(XVII)  $(C_2-C_8)$ -alkynyl; or  
(XVIII) H, or a pharmaceutically acceptable salt  
thereof.

50. (Original) The method of claim 49, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 0.1nM to about 200 $\mu$ M.

51. (Original) The method of claim 50, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 10nM to about 100 $\mu$ M.

52. (Original) The method of claim 51, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 100nM to about 50 $\mu$ M.

53. (Original) The method of claim 52, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 1 $\mu$ M to about 10 $\mu$ M.

54. (Currently Amended) The method of claim 49, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 0.1 to about 1000 mg/day.

55. (Currently Amended) The method of claim 49, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 15 to about 1500 mg/day.

56. (Currently Amended) The method of claim 55, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 1 to about 100 mg/day.

57. (Currently Amended) The method of claim 56, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 5 to about 50 mg/day.

58. (Original) The method of claim 49, wherein said disease is Alzheimer's disease.

59. (Currently Amended) The method of claim 49, wherein said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage Hemorrhage with Amyloidosis of the Dutch Type.

60-98. (Canceled)

99. (New) A method according to claim 49, wherein the compound is

N-[(1*S*, 2*S*, 4*R*)-1-(3,5-Difluorobenzyl)-4-(*syn*, *syn*)-(3,5-dimethoxycyclohexylcarbamoyl)-2-hydroxyhexyl]-*N,N*-dipropylisophthalamide;

N-[4-(*R*)-(Cyclohexylmethyl-carbamoyl)-1-(*S*)-(3,5-difluorobenzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide;

4-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-4-(*S*)-hydroxy-2-(*R*)-methyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-4-(*S*)-hydroxy-2-(*R*)-propyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-4-(*S*)-hydroxyl-2-(*R*)-isobutyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([2-(*R*)-Benzyl-6-(3,5-difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid;

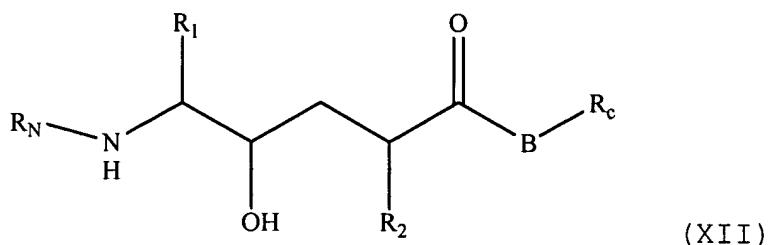
4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester;

4-(*anti*)-{[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-methyl}cyclohexanecarboxylic acid;

N-[*(1S, 2S, 4R)*-1-(3,5-Difluorobenzyl)-4-(*syn, syn*)-(3,5-dimethoxycyclohexylcarbamoyl)-2-hydroxyhexyl]-*N,N*-dipropylisophthalamide; or

*N*-[4-(*R*)-(Adamantan-2-ylcarbamoyl)-1-(*S*)-(3,5-difluorobenzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide.

100. (New) A method for treating Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type comprising administering an effective amount of the formula



where R<sub>1</sub> is:

- (I) C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted or substituted with one, two or three C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -NH<sub>2</sub>, -C≡N, -CF<sub>3</sub>, or -N<sub>3</sub>,
- (II) -(CH<sub>2</sub>)<sub>1-2</sub>-S-CH<sub>3</sub>,

(III)  $-\text{CH}_2\text{-CH}_2\text{-S-CH}_3$ ,

(IV)  $-\text{CH}_2\text{-}(\text{C}_2\text{-C}_6 \text{ alkenyl})$  unsubstituted or substituted by one  $-\text{F}$ ,

(V)  $-(\text{CH}_2)_{0-3}\text{-}(\text{R}_1\text{-aryl})$  where  $\text{R}_1\text{-aryl}$  is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl unsubstituted or substituted on the aryl ring with one or two of the following substituents which can be the same or different:

- (A)  $\text{C}_1\text{-C}_3$  alkyl,
- (B)  $-\text{CF}_3$ ,
- (C)  $-\text{F}$ ,  $\text{Cl}$ ,  $-\text{Br}$  and  $-\text{I}$ ,
- (D)  $\text{C}_1\text{-C}_3$  alkoxy,
- (E)  $-\text{O-CF}_3$ ,
- (F)  $-\text{NH}_2$ ,
- (G)  $-\text{OH}$ , or
- (H)  $-\text{C}\equiv\text{N}$ ,

(VI)  $-(\text{CH}_2)_{n_1}\text{-}(\text{R}_1\text{-heteroaryl})$  where  $n_1$  is 0, 1, 2, or 3 and  $\text{R}_1\text{-heteroaryl}$  is:

- (A) pyridinyl,
- (B) pyrimidinyl,
- (C) quinolinyl,
- (D) indenyl,
- (E) indanyl,
- (F) benzothiophenyl,
- (G) indolyl,
- (H) indolinyl,
- (I) pyridazinyl,
- (J) pyrazinyl,
- (K) isoindolyl,
- (L) isoquinolyl,

- (M) quinazolinyl,
- (N) quinoxalinyt,
- (O) phthalazinyl,
- (P) imidazolyl,
- (Q) isoxazolyl,
- (R) pyrazolyl,
- (S) oxazolyl,
- (T) thiazolyl,
- (U) indolizinyl,
- (V) indazolyl,
- (W) benzothiazolyl,
- (X) benzimidazolyl,
- (Y) benzofuranyl,
- (Z) furanyl,
- (AA) thietyl,
- (BB) pyrrolyl,
- (CC) oxadiazolyl,
- (DD) thiadiazolyl,
- (EE) triazolyl,
- (FF) tetrazolyl,
- (GG) 1, 4-benzodioxan
- (HH) purinyl,
- (II) oxazolopyridinyl,
- (JJ) imidazopyridinyl,
- (KK) isothiazolyl,
- (LL) naphthyridinyl,
- (MM) cinnolinyl,
- (NN) carbazolyl,
- (OO)  $\beta$ -carbolinyl,
- (PP) isochromanyl,
- (QQ) chromanyl,

- (RR) furazanyl,
- (SS) tetrahydroisoquinoline,
- (TT) isoindolinyl,
- (UU) isobenzotetrahydrofuranyl,
- (VV) isobenzotetrahydrothienyl,
- (WW) isobenzothiophenyl,
- (XX) benzoxazolyl, or
- (YY) pyridopyridinyl,

where the R<sub>1</sub>-heteroaryl group is bonded to -(CH<sub>2</sub>)<sub>0-3</sub>- by any ring atom of the parent R<sub>N</sub>-heteroaryl group substituted by hydrogen such that the new bond to the R<sub>1</sub>-heteroaryl group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

- (1) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (2) -CF<sub>3</sub>,
- (3) -F, Cl, -Br, or -I,
- (4) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (5) -O-CF<sub>3</sub>,
- (6) -NH<sub>2</sub>,
- (7) -OH, or
- (8) -C≡N,

with the proviso that when n<sub>1</sub> is zero R<sub>1</sub>-heteroaryl is not bonded to the carbon chain by nitrogen, or

(VII) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1</sub>-heterocycle) where n<sub>1</sub> is as defined above and

R<sub>1</sub>-heterocycle is:

- (A) morpholinyl,
- (B) thiomorpholinyl,
- (C) thiomorpholinyl S-oxide,
- (D) thiomorpholinyl S,S-dioxide,
- (E) piperazinyl,

- (F) homopiperazinyl,
- (G) pyrrolidinyl,
- (H) pyrrolinyl,
- (I) tetrahydropyranyl,
- (J) piperidinyl,
- (K) tetrahydrofuranyl, or
- (L) tetrahydrothiophenyl,

where the R<sub>1</sub>-heterocycle group is bonded by any atom of the parent R<sub>1</sub>-heterocycle group substituted by hydrogen such that the new bond to the R<sub>1</sub>-heteroaryl group replaces the hydrogen atom and its bond, where heterocycle is unsubstituted or substituted with one or two:

- (1) =O,
- (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (3) -CF<sub>3</sub>,
- (4) -F, Cl, -Br and -I,
- (5) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (6) -O-CF<sub>3</sub>,
- (7) -NH<sub>2</sub>,
- (8) -OH, or
- (9) -C≡N,

with the proviso that when n<sub>1</sub> is zero R<sub>1</sub>-heterocycle is not bonded to the carbon chain by nitrogen;

where R<sub>2</sub> is:

- (I) -H,
- (II) C<sub>1</sub>-C<sub>6</sub> alkyl, or
- (III) -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>2-1</sub> where R<sub>2-1</sub> is (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, R<sub>1</sub>-aryl or R<sub>1</sub>-heteroaryl where R<sub>1</sub>-aryl and R<sub>1</sub>-heteroaryl are as defined above,

where R<sub>N</sub> is:

- (I) R<sub>N-1</sub>-X<sub>N</sub>- where X<sub>N</sub> is:

- (A) -CO-,
- (B) -SO<sub>2</sub>-,
- (C) -(CR'R'')<sub>1-6</sub> where R' and R'' are the same or different and are -H or C<sub>1</sub>-C<sub>4</sub> alkyl,
- (D) -CO-(CR'R'')<sub>1-6</sub>-X<sub>N-1</sub> where X<sub>N-1</sub> is -O-, -S- and -NR'R''- and where R' and R'' are as defined above,
- (E) a single bond;

where R<sub>N-1</sub> is:

- (A) R<sub>N</sub>-aryl where R<sub>N</sub>-aryl is phenyl, 1-naphthyl and 2-naphthyl unsubstituted or substituted with one, two, three or four of the following substituents which can be the same or different and are:
  - (1) C<sub>1</sub>-C<sub>6</sub> alkyl,
  - (2) -F, -Cl, -Br, or -I,
  - (3) -OH,
  - (4) -NO<sub>2</sub>,
  - (5) -CO-OH,
  - (6) -C≡N,
  - (7) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are the same or different and are:
    - (a) -H,
    - (b) -C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with one
      - (i) -OH, or
      - (ii) -NH<sub>2</sub>,
    - (c) -C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with one to three -F, -Cl, -Br, or -I,
    - (d) -C<sub>3</sub>-C<sub>7</sub> cycloalkyl,

(e)  $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl}),$   
(f)  $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl}),$   
(g)  $-C_1-C_6 \text{ alkenyl with one or two}$   
double bonds,  
(h)  $-C_1-C_6 \text{ alkynyl with one or two}$   
triple bonds,  
(i)  $-C_1-C_6 \text{ alkyl chain with one double}$   
bond and one triple bond,  
(j)  $-R_1\text{-aryl where } R_1\text{-aryl is as defined}$   
above, or  
(k)  $-R_1\text{-heteroaryl where } R_1\text{-heteroaryl is as}$   
defined above,  
(8)  $-CO-(C_3-C_{12} \text{ alkyl}),$   
(9)  $-CO-(C_3-C_6 \text{ cycloalkyl}),$   
(10)  $-CO-R_1\text{-heteroaryl where } R_1\text{-heteroaryl is as}$   
defined above,  
(11)  $-CO-R_1\text{-heterocycle where } R_1\text{-heterocycle is as}$   
defined above,  
(12)  $-CO-R_{N-4} \text{ where } R_{N-4} \text{ is morpholinyl,}$   
thiomorpholinyl, piperazinyl, piperidinyl  
or pyrrolidinyl where each group is  
unsubstituted or substituted with one or  
two  $C_1-C_3 \text{ alkyl},$   
(13)  $-CO-O-R_{N-5} \text{ where } R_{N-5} \text{ is:}$   
(a)  $C_1-C_6 \text{ alkyl, or}$   
(b)  $-(CH_2)_{0-2}-(R_1\text{-aryl}) \text{ where } R_1\text{-aryl is as}$   
defined above,  
(14)  $-SO_2-NR_{N-2}R_{N-3} \text{ where } R_{N-2} \text{ and } R_{N-3} \text{ are as}$   
defined above,  
(15)  $-SO-(C_1-C_8 \text{ alkyl}),$   
(16)  $-SO_2-(C_3-C_{12} \text{ alkyl}),$

(17) -NH-CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(18) -NH-CO-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(19) -N-CS-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(20) -N(C<sub>1</sub>-C<sub>3</sub> alkyl)-CO-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(21) -NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> can be the same or different and are as defined above,

(22) -R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,

(23) -O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),

(24) -O-CO-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(25) -O-CS-N(C<sub>1</sub>-C<sub>3</sub> alkyl)<sub>2</sub>,

(26) -O-(C<sub>1</sub>-C<sub>6</sub> alkyl),

(27) -O-(C<sub>2</sub>-C<sub>5</sub> alkyl)-COOH,

(28) -S-(C<sub>1</sub>-C<sub>6</sub> alkyl),

(29) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 -F,

(30) -O-(C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted with 1, 2, 3, 4, or 5 -F, or

(31) -O-Φ,

(B) -R<sub>N-heteroaryl</sub> where R<sub>N-heteroaryl</sub> is:

- (A) pyridinyl,
- (B) pyrimidinyl,
- (C) quinolinyl,
- (D) indenyl,
- (E) indanyl,
- (F) benzothiophenyl,
- (G) indolyl,
- (H) indolinyl,
- (I) pyridazinyl,

- (J) pyrazinyl,
- (K) isoindolyl,
- (L) isoquinolyl,
- (M) quinazolinyl,
- (N) quinoxalinyln,
- (O) phthalazinyl,
- (P) imidazolyl,
- (Q) isoxazolyl,
- (R) pyrazolyl,
- (S) oxazolyl,
- (T) thiazolyl,
- (U) indolizinyl,
- (V) indazolyl,
- (W) benzothiazolyl,
- (X) benzimidazolyl,
- (Y) benzofuranyl,
- (Z) furanyl,
- (AA) thienyl,
- (BB) pyrrolyl,
- (CC) oxadiazolyl,
- (DD) thiadiazolyl,
- (EE) triazolyl,
- (FF) tetrazolyl,
- (GG) 1, 4-benzodioxan
- (HH) purinyl,
- (II) oxazolopyridinyl,
- (JJ) imidazopyridinyl,
- (KK) isothiazolyl,
- (LL) naphthyridinyl,
- (MM) cinnolinyl,
- (NN) carbazolyl,

- (OO)  $\beta$ -carbolinyl,
- (PP) isochromanyl,
- (QQ) chromanyl,
- (RR) furazanyl,
- (SS) tetrahydroisoquinoline,
- (TT) isoindolinyl,
- (UU) isobenzotetrahydrofuranyl,
- (VV) isobenzotetrahydrothienyl,
- (WW) isobenzothiophenyl,
- (XX) benzoxazolyl, or
- (YY) pyridopyridinyl,

where the  $R_N$ -heteroaryl group is bonded by any atom of the parent  $R_N$ -heteroaryl group substituted by hydrogen such that the new bond to the  $R_N$ -heteroaryl group replaces the hydrogen atom and its bond, where heteroaryl is unsubstituted or substituted with one or two:

- (1)  $C_1-C_6$  alkyl,
- (2) -F, -Cl, -Br, or -I,
- (3) -OH,
- (4) -NO<sub>2</sub>,
- (5) -CO-OH,
- (6) -C≡N,
- (7) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are the same or different and are:
  - (a) -H,
  - (b) - $C_1-C_6$  alkyl unsubstituted or substituted with one
    - (i) -OH, or
    - (ii) -NH<sub>2</sub>,

(c)  $-C_1-C_6$  alkyl unsubstituted or substituted with 1, 2, or 3 -F, -Cl, -Br, or -I,  
(d)  $-C_3-C_7$  cycloalkyl,  
(e)  $-(C_1-C_2$  alkyl) $-(C_3-C_7$   
cycloalkyl),  
(f)  $-(C_1-C_6$  alkyl)-O- $(C_1-C_3$  alkyl),  
(g)  $-C_1-C_6$  alkenyl with one or two double bonds,  
(h)  $-C_1-C_6$  alkynyl with one or two triple bonds,  
(i)  $-C_1-C_6$  alkyl chain with one double bond and one triple bond,  
(j)  $-R_1\text{-aryl}$  where  $R_1\text{-aryl}$  is as defined above, or  
(k)  $-R_1\text{-heteroaryl}$  where  $R_1\text{-heteroaryl}$  is as defined above,  
(8)  $-CO-(C_3-C_{12}$  alkyl),  
(9)  $-CO-(C_3-C_6$  cycloalkyl),  
(10)  $-CO-R_1\text{-heteroaryl}$  where  $R_1\text{-heteroaryl}$  is as defined above,  
(11)  $-CO-R_1\text{-heterocycle}$  where  $R_1\text{-heterocycle}$  is as defined above,  
(12)  $-CO-R_{N-4}$  where  $R_{N-4}$  is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or pyrrolidinyl where each group is unsubstituted or substituted with one or two  $C_1-C_3$  alkyl,  
(13)  $-CO-O-R_{N-5}$  where  $R_{N-5}$  is:  
(a)  $C_1-C_6$  alkyl, or

(b)  $-(CH_2)_{0-2}-$ (R<sub>1-aryl</sub>) where R<sub>1-aryl</sub> is as defined above,

(14) -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,

(15) -SO-(C<sub>1-C<sub>8</sub></sub> alkyl),

(16) -SO<sub>2</sub>-(C<sub>3-C<sub>12</sub></sub> alkyl),

(17) -NH-CO-O-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(18) -NH-CO-N(C<sub>1-C<sub>3</sub></sub> alkyl)<sub>2</sub>,

(19) -N-CS-N(C<sub>1-C<sub>3</sub></sub> alkyl)<sub>2</sub>,

(20) -N(C<sub>1-C<sub>3</sub></sub> alkyl)-CO-R<sub>N-5</sub> where R<sub>N-5</sub> is as defined above,

(21) -NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> can be the same or different and are as defined above,

(22) -R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,

(23) -O-CO-(C<sub>1-C<sub>6</sub></sub> alkyl),

(24) -O-CO-N(C<sub>1-C<sub>3</sub></sub> alkyl)<sub>2</sub>,

(25) -O-CS-N(C<sub>1-C<sub>3</sub></sub> alkyl)<sub>2</sub>,

(26) -O-(C<sub>1-C<sub>6</sub></sub> alkyl),

(27) -O-(C<sub>2-C<sub>5</sub></sub> alkyl)-COOH, or

(28) -S-(C<sub>1-C<sub>6</sub></sub> alkyl),

(C) -R<sub>N-aryl</sub>-R<sub>N-aryl</sub> where -R<sub>N-aryl</sub> is as defined above,

(D) -R<sub>N-aryl</sub>-R<sub>N-heteroaryl</sub> where -R<sub>N-aryl</sub> and -R<sub>N-heteroaryl</sub> are as defined above,

(E) -R<sub>N-heteroaryl</sub>-R<sub>N-aryl</sub> where -R<sub>N-aryl</sub> and -R<sub>N-heteroaryl</sub> are as defined above,

(F) -R<sub>N-heteroaryl</sub>-R<sub>N-heteroaryl</sub> where R<sub>N-heteroaryl</sub> is as defined above,

(G)  $-R_N\text{-aryl}-O-R_N\text{-aryl}$  where  $-R_N\text{-aryl}$  is as defined above,

(H)  $-R_N\text{-aryl}-S-R_N\text{-aryl}$  where  $-R_N\text{-aryl}$  is as defined above,

(I)  $-R_N\text{-heteroaryl}-O-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(J)  $-R_N\text{-heteroaryl}-S-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(K)  $-R_N\text{-aryl}-CO-R_N\text{-aryl}$  where  $-R_N\text{-aryl}$  is as defined above,

(L)  $-R_N\text{-aryl}-CO-R_N\text{-heteroaryl}$  where  $-R_N\text{-aryl}$  and  $R_N\text{-heteroaryl}$  are as defined above,

(M)  $-R_N\text{-aryl}-SO_2-R_N\text{-aryl}$  where  $-R_N\text{-aryl}$  is as defined above,

(N)  $-R_N\text{-heteroaryl}-CO-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(O)  $-R_N\text{-heteroaryl}-SO_2-R_N\text{-heteroaryl}$  where  $R_N\text{-heteroaryl}$  is as defined above,

(P)  $-R_N\text{-aryl}-O-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-aryl}$  is as defined above,

(Q)  $-R_N\text{-aryl}-S-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-aryl}$  is as defined above,

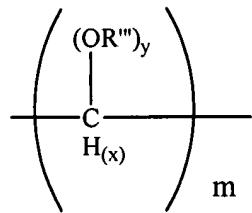
(R)  $-R_N\text{-heteroaryl}-O-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-heteroaryl}$  is as defined above, or

(S)  $-R_N\text{-heteroaryl}-S-(C_1-C_8 \text{ alkyl})-\phi$  where  $R_N\text{-heteroaryl}$  is as defined above,

(II)  $A-X_N-$  where  $X_N$  is  $-CO-$ ,

wherein A is

(A)  $-T-E-(Q)_m-$ ,  
(1) where  $-T$  is



where

- (a)  $x = 1$  when  $y = 1$  and  $x = 2$  when  $y = 0$ ,
- (b)  $m$  is 0, 1, 2 or 3,
- (c) the values of  $x$  and  $y$  vary independently on each carbon when  $m$  is 2 and 3, and
- (d)  $R'''$  varies independently on each carbon and is H, ( $C_1-C_2$ ) alkyl, phenyl, or phenyl( $C_1-C_3$ )alkyl;

(2) -E is

- (a)  $C_1-C_5$  alkyl, but only if  $m'$  does not equal 0,
- (b) methylthioxy( $C_2-C_4$ )alkyl,
- (c) an aryl group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,
- (d) a heterocyclic group having 5 to 7 atoms when monocyclic or having 8 to 12 atoms when fused,
- (e) a mono or fused ring cycloalkyl group having 5 to 10 carbon atoms,
- (f) biphenyl,
- (g) diphenyl ether,
- (h) diphenylketone,
- (i) phenyl( $C_1-C_8$ )alkyloxyphenyl, or

(j) C<sub>1</sub>-C<sub>6</sub> alkoxy;

(3) -Q is

(a) C<sub>1</sub>-C<sub>3</sub> alkyl,

(b) C<sub>1</sub>-C<sub>3</sub> alkoxy,

(c) C<sub>1</sub>-C<sub>3</sub> alkylthioxy,

(d) C<sub>1</sub>-C<sub>6</sub> alkylacylamino,

(e) C<sub>1</sub>-C<sub>6</sub> alkylacyloxy,

(f) amido (including primary, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl secondary and tertiary amino moieties),

(g) C<sub>1</sub>-C<sub>6</sub> alkylamino

(h) phenylamino,

(i) carbamyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl amides and esters),

(j) carboxyl (including C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl esters),

(k) carboxy(C<sub>2</sub>-C<sub>5</sub>) alkoxy,

(l) carboxy(C<sub>2</sub>-C<sub>5</sub>) alkylthioxy,

(m) heterocyclacyl,

(n) heteroarylacyl, or

(o) hydroxyl;

(4) m' is 0, 1, 2 or 3;

(B) -E(Q)<sub>m''</sub>, wherein E and -Q are as defined as above and m'' is 0, 1, 2, or 3;

(C) -T-E wherein -E and -Q are as defined as above; or

(D) -E wherein -E is as defined as above;

(III) -CO-(C<sub>1</sub>-C<sub>6</sub> alkyl) where alkyl is unsubstituted or substituted with one or two:

(A) -OH,

- (B)  $-C_1-C_6$  alkoxy,
- (C)  $-C_1-C_6$  thioalkoxy,
- (D)  $-CO-O-R_{N-8}$  where  $R_{N-8}$  is  $-H$ ,  $C_1-C_6$  alkyl or  $-\phi$ ,
- (E)  $-CO-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,
- (F)  $-CO-R_{N-4}$  where  $R_{N-4}$  is as defined above,
- (G)  $-SO_2-(C_1-C_8$  alkyl),
- (H)  $-SO_2-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,
- (I)  $-NH-CO-(C_1-C_6$  alkyl),
- (J)  $-NH-CO-O-R_{N-8}$  where  $R_{N-8}$  is as defined above,
- (K)  $-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,
- (L)  $-R_{N-4}$  where  $R_{N-4}$  is as defined above,
- (M)  $-O-CO-(C_1-C_6$  alkyl),
- (N)  $-O-CO-NR_{N-8}R_{N-8}$  where the  $R_{N-8}$  is the same or different and are as defined above, or
- (O)  $-O-(C_1-C_5$  alkyl)-COOH,

(IV)  $-CO-(C_1-C_3$  alkyl)-O-( $C_1-C_3$  alkyl) where alkyl is unsubstituted or substituted with one or two

- (A)  $-OH$ ,
- (B)  $-C_1-C_6$  alkoxy,
- (C)  $-C_1-C_6$  thioalkoxy,
- (D)  $-CO-O-R_{N-8}$  where  $R_{N-8}$  is  $-H$ ,  $C_1-C_6$  alkyl or  $-\phi$ ,
- (E)  $-CO-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,
- (F)  $-CO-R_{N-4}$  where  $R_{N-4}$  is as defined above,
- (G)  $-SO_2-(C_1-C_8$  alkyl),
- (H)  $-SO_2-NR_{N-2}R_{N-3}$  where  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are as defined above,
- (I)  $-NH-CO-(C_1-C_6$  alkyl),

- (J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{N-8}$  where  $\text{R}_{N-8}$  is as defined above,
- (K)  $-\text{NR}_{N-2}\text{R}_{N-3}$  where  $\text{R}_{N-2}$  and  $\text{R}_{N-3}$  are the same or different and are as defined above,
- (L)  $-\text{R}_{N-4}$  where  $\text{R}_{N-4}$  is as defined above,
- (M)  $-\text{O}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$
- (N)  $-\text{O}-\text{CO}-\text{NR}_{N-8}\text{R}_{N-8}$  where the  $\text{R}_{N-8}$  are the same or different and are as defined above, or
- (O)  $-\text{O}- (\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH},$
- (V)  $-\text{CO}- (\text{C}_1-\text{C}_3 \text{ alkyl})-\text{S}- (\text{C}_1-\text{C}_3 \text{ alkyl})$  where alkyl is unsubstituted or substituted with one or two
  - (A)  $-\text{OH},$
  - (B)  $-\text{C}_1-\text{C}_6 \text{ alkoxy},$
  - (C)  $-\text{C}_1-\text{C}_6 \text{ thioalkoxy},$
  - (D)  $-\text{CO}-\text{O}-\text{R}_{N-8}$  where  $\text{R}_{N-8}$  is  $-\text{H}$ ,  $\text{C}_1-\text{C}_6$  alkyl or  $-\phi,$
  - (E)  $-\text{CO}-\text{NR}_{N-2}\text{R}_{N-3}$  where  $\text{R}_{N-2}$  and  $\text{R}_{N-3}$  are the same or different and are as defined above,
  - (F)  $-\text{CO}-\text{R}_{N-4}$  where  $\text{R}_{N-4}$  is as defined above,
  - (G)  $-\text{SO}_2- (\text{C}_1-\text{C}_8 \text{ alkyl}),$
  - (H)  $-\text{SO}_2-\text{NR}_{N-2}\text{R}_{N-3}$  where  $\text{R}_{N-2}$  and  $\text{R}_{N-3}$  are the same or different and are as defined above,
  - (I)  $-\text{NH}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$
  - (J)  $-\text{NH}-\text{CO}-\text{O}-\text{R}_{N-8}$  where  $\text{R}_{N-8}$  is as defined above,
  - (K)  $-\text{NR}_{N-2}\text{R}_{N-3}$  where  $\text{R}_{N-2}$  and  $\text{R}_{N-3}$  are the same or different and are as defined above,
  - (L)  $-\text{R}_{N-4}$  where  $\text{R}_{N-4}$  is as defined above,
  - (M)  $-\text{O}-\text{CO}- (\text{C}_1-\text{C}_6 \text{ alkyl}),$
  - (N)  $-\text{O}-\text{CO}-\text{NR}_{N-8}\text{R}_{N-8}$  where the  $\text{R}_{N-8}$  are the same or different and are as defined above, or
  - (O)  $-\text{O}- (\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH},$

(VI)  $-\text{CO}-\text{CH}(-( \text{CH}_2 )_{0-2}-\text{O}-\text{R}_{\text{N}-10})-( \text{CH}_2 )_{0-2}-\text{R}_{\text{N}-\text{aryl}}/\text{R}_{\text{N}-\text{heteroaryl}}$

where  $\text{R}_{\text{N}-\text{aryl}}$  and  $\text{R}_{\text{N}-\text{heteroaryl}}$  are as defined above,

where  $\text{R}_{\text{N}-10}$  is:

- (A) -H,
- (B)  $\text{C}_1\text{-C}_6$  alkyl,
- (C)  $\text{C}_3\text{-C}_7$  cycloalkyl,
- (D)  $\text{C}_2\text{-C}_6$  alkenyl with one double bond,
- (E)  $\text{C}_2\text{-C}_6$  alkynyl with one triple bond,
- (F)  $\text{R}_{\text{l}-\text{aryl}}$  where  $\text{R}_{\text{l}-\text{aryl}}$  is as defined above, or
- (G)  $\text{R}_{\text{N}-\text{heteroaryl}}$  where  $\text{R}_{\text{N}-\text{heteroaryl}}$  is as defined

above;

where B is -O-, -NH-, or  $-\text{N}(\text{C}_1\text{-C}_6\text{ alkyl})-$ ;

where  $\text{R}_{\text{c}}$  is:

(I)  $-(\text{C}_1\text{-C}_{10})\text{alkyl-K}_{1-3}$  in which:

- (A) the alkyl chain is unsubstituted or substituted with one -OH,
- (B) the alkyl chain is unsubstituted or substituted with one  $\text{C}_1\text{-C}_6$  alkoxy unsubstituted or substituted with 1-5 -F,
- (C) the alkyl chain is unsubstituted or substituted with one  $-\text{O}-\phi$ ,
- (D) the alkyl chain is unsubstituted or substituted with 1-5 -F,
- (E) the alkyl chain is unsubstituted or substituted with a combination of up to three atoms of oxygen and sulfur each such atom replacing one carbon,
- (F) each K is:
  - (1) H,
  - (2)  $\text{C}_1\text{-C}_3$  alkyl,
  - (3)  $\text{C}_1\text{-C}_3$  alkoxy,

- (4) C<sub>1</sub>-C<sub>3</sub> alkylthioxy,
- (5) C<sub>1</sub>-C<sub>6</sub> alkylacylamino,
- (6) C<sub>1</sub>-C<sub>6</sub> alkylacyloxy,
- (7) amido
- (8) C<sub>1</sub>-C<sub>6</sub> alkylamino
- (9) phenylamino,
- (10) carbamyl
- (11) carboxyl
- (12) carboxy(C<sub>2</sub>-C<sub>5</sub>) alkoxy,
- (13) carboxy(C<sub>2</sub>-C<sub>5</sub>) alkylthioxy,
- (14) heterocyclacyl,
- (15) heteroarylacyl,
- (16) amino unsubstituted or substituted with C<sub>1</sub>-C<sub>6</sub> alkyl,
- (17) hydroxyl, or
- (18) carboxyl methyl ester;

(II) - (CH<sub>2</sub>)<sub>0-3</sub>-J-[(-(CH<sub>2</sub>)<sub>0-3</sub>-K]<sub>1-3</sub> where K is as defined above and J is:

- (A) a 5 to 7 atom monocyclic aryl group,
- (B) a 8 to 12 atom multicyclic aryl group,
- (C) a 5 to 7 atom heterocyclic group,
- (D) a 8 to 12 atom multicyclic heterocyclic group, or
- (E) a 5 to 10 atom monocyclic or multicyclic cycloalkyl group;

(III) - (CH<sub>2</sub>)<sub>0-3</sub>- (C<sub>3</sub>-C<sub>7</sub>) cycloalkyl where cycloalkyl can be unsubstituted or substituted with one, two or three

- (A) C<sub>1</sub>-C<sub>3</sub> alkyl unsubstituted or substituted with 1, 2, 3, or 4 -F,

-Cl, -Br, or -I,  
(B) -CO-OH,  
(C) -CO-O- (C<sub>1</sub>-C<sub>4</sub> alkyl),  
(D) -OH, or  
(E) C<sub>1</sub>-C<sub>6</sub> alkoxy,  
(IV) -(CH<sub>2</sub>)<sub>2-6</sub>-OH,  
(V) -(CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C</sub>-aryl where R<sub>C-x</sub> and R<sub>C-y</sub> are -H, C<sub>1</sub>-C<sub>4</sub> alkyl and φ- and R<sub>C</sub>-aryl is the same as R<sub>N</sub>-aryl,  
(VI) -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>C</sub>-heteroaryl where R<sub>C</sub>-heteroaryl is:  
(A) pyridinyl,  
(B) pyrimidinyl,  
(C) quinolinyl,  
(D) indenyl,  
(E) indanyl,  
(F) benzothiophenyl,  
(G) indolyl,  
(H) indolinyl,  
(I) pyridazinyl,  
(J) pyrazinyl,  
(K) isoindolyl,  
(L) isoquinolyl,  
(M) quinazolinyl,  
(N) quinoxalinyl,  
(O) phthalazinyl,  
(P) isoxazolyl,  
(Q) pyrazolyl,  
(R) indolizinyl,  
(S) indazolyl,  
(T) benzothiazolyl,  
(U) benzimidazolyl,  
(V) benzofuranyl,

(W) furanyl,  
(X) thienyl,  
(Y) pyrrolyl,  
(Z) oxadiazolyl,  
(AA) thiadiazolyl,  
(BB) triazolyl,  
(CC) tetrazolyl,  
(DD) 1, 4-benzodioxan  
(EE) purinyl,  
(FF) oxazolopyridinyl,  
(GG) imidazopyridinyl,  
(HH) isothiazolyl,  
(II) naphthyridinyl,  
(JJ) cinnolinyl,  
(KK) carbazolyl,  
(LL)  $\beta$ -carbolinyl,  
(MM) isochromanyl,  
(NN) chromanyl,  
(OO) furazanyl,  
(PP) tetrahydroisoquinoline,  
(QQ) isoindolinyl,  
(RR) isobenzotetrahydrofuranyl,  
(SS) isobenzotetrahydrothienyl,  
(TT) isobenzothiophenyl,  
(UU) benzoxazolyl, or  
(VV) pyridopyridinyl,

(VII)  $-(CH_2)_{0-4}-R_c$ -heterocycle where  $R_c$ -heterocycle is the same as  $R_1$ -heterocycle,

(VIII)  $-C(R_{c-1})(R_{c-2})-CO-NH-R_{c-3}$  where  $R_{c-1}$  and  $R_{c-2}$  are the same or different and are:

(A) -H,

(B) -C<sub>1</sub>-C<sub>6</sub> alkyl,

(C) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C'-aryl</sub> where R<sub>C'-aryl</sub> is as defined above for

R<sub>1-aryl</sub>,

(D) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> is as defined above,

(E) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heterocycle</sub> where R<sub>C-heterocycle</sub> is as defined above,

(F) -R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> is as defined above,

(G) -R<sub>C-heterocycle</sub> where R<sub>C-heterocycle</sub> is as defined above,

(H) -(CH<sub>2</sub>)<sub>1-4</sub>-OH,

(I) -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C-4</sub>-(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C'-aryl</sub> where R<sub>C-4</sub> is -O-, -S-, -NH- or

-NHR<sub>C-5-</sub> where R<sub>C-5</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, and where R<sub>C'-aryl</sub> is as defined above,

(J) -(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C-4</sub>-(CH<sub>2</sub>)<sub>1-4</sub>-R<sub>C-heteroaryl</sub> where R<sub>C-4</sub> and R<sub>C-heteroaryl</sub> are as defined above, or

(K) -R<sub>C'-aryl</sub> where R<sub>C'-aryl</sub> is as defined above,  
and where R<sub>C-3</sub> is:

(A) -H,

(B) -C<sub>1</sub>-C<sub>6</sub> alkyl,

(C) -R<sub>C'-aryl</sub> where R<sub>C'-aryl</sub> is as defined above,

(D) -R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> is as defined above,

(E) -R<sub>C-heterocycle</sub> where R<sub>C-heterocycle</sub> is as defined above,

(F) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C'-aryl</sub> where R<sub>C'-aryl</sub> is as defined above,

(G) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> is as defined above, or

(H) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heterocycle</sub> where R<sub>C-heterocycle</sub> is as defined above,

(IX) -CH(Φ)<sub>2</sub>,

(X) -cyclopentyl or -cyclohexyl ring fused to a phenyl or heteroaryl ring where heteroaryl is as defined above and phenyl and heteroaryl are unsubstituted or substituted with one, two or three:

- (A) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (B) -CF<sub>3</sub>,
- (C) -F, Cl, -Br and -I,
- (D) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (E) -OCF<sub>3</sub>,
- (F) -NH<sub>2</sub>,
- (G) -OH, or
- (H) -C≡N,

(XI) -CH<sub>2</sub>-C≡CH;

(XII) -(CH<sub>2</sub>)<sub>0-1</sub>-CHR<sub>C-5</sub>-(CH<sub>2</sub>)<sub>0-1</sub>-Φ where R<sub>C-5</sub> is:

- (A) -OH, or
- (B) -CH<sub>2</sub>-OH;

(XIII) -CH(-Φ)-CO-O(C<sub>1</sub>-C<sub>3</sub> alkyl);

(XIV) -CH(-CH<sub>2</sub>-OH)-CH(-OH)-Φ-NO<sub>2</sub>;

(XV) -(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-OH;

(XVI) -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(-O-CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>;

(XVII) -(C<sub>2</sub>-C<sub>8</sub>) alkynyl; or

(XVIII) -H; or a pharmaceutically acceptable salt thereof.

101. (New) The method of claim 100, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 0.1nM to about 200 $\mu$ M.

102. (New) The method of claim 101, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 10nM to about 100 $\mu$ M.

103. (New) The method of claim 101, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 100nM to about 50 $\mu$ M.

104. (New) The method of claim 103, wherein said compound inhibits 50% of the enzyme's activity at a concentration of from about 1 $\mu$ M to about 10 $\mu$ M.

105. (New) The method of claim 100, wherein said therapeutic amount is in the range of from about 0.1 to about 1000 mg/day.

106. (New) The method of claim 100, wherein said therapeutic amount is in the range of from about 15 to about 1500 mg/day.

107. (New) The method of claim 106, wherein said therapeutic amount is in the range of from about 1 to about 100 mg/day.

108. (New) The method of claim 107, wherein said therapeutic amount is in the range of from about 5 to about 50 mg/day.

109. (New) The method according to claim 100, wherein the compound is

N-[*(1S, 2S, 4R)*-1-(3,5-Difluorobenzyl)-4-(*syn, syn*)-(3,5-dimethoxycyclohexylcarbamoyl)-2-hydroxyhexyl]-*N,N*-dipropylisophthalamide,

6-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-hexanoic acid,

5-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-pentanoic acid,

4-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-butyric acid,

3-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-propionic acid,

8-[6-(3,5-Difluorophenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxyhexanoylamino]-octanoic acid,

8-[6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoylbenzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-octanoic acid methyl ester,

*N*-[4-(*R*)-Butylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-isobutylcarbamoyl-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-(Cyclohexylmethyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(piperidine-1-carbonyl)-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(2-dimethylaminoethylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-(Butyl-methyl-carbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(3-hydroxy-propylcarbamoyl)-hexyl]-*N,N*-dipropyl-isophthalamide,

4-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(3-dimethylamino-propylcarbamoyl)-2-(*S*)-hydroxy-hexyl]-*N,N*-dipropyl-isophthalamide,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-methyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-2-(*R*)-propyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxyl-2-(*R*)-isobutyl-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([2-(*R*)-Benzyl-6-(3,5-difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-benzoylamino)-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid,

4-(*anti*)-([6-(3,5-Difluoro-phenyl)-5-(*S*)-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-(*R*)-ethyl-4-(*S*)-hydroxy-hexanoylamino]-methyl)-cyclohexanecarboxylic acid methyl ester,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(2-morpholin-4-yl-ethylcarbamoyl)-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-isobutylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-(2-Diethylamino-ethylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-(Adamantan-2-ylcarbamoyl)-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-methyl-5-morpholin-4-yl-5-oxo-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[4-(*R*)-Benzylcarbamoyl-1-(*S*)-(3,5-difluoro-benzyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-(4-fluoro-benzylcarbamoyl)-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-phenethylcarbamoyl-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide,

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-4-(*R*)-[(furan-2-ylmethyl)-carbamoyl]-2-(*S*)-hydroxy-pentyl]-5-methyl-*N,N*-dipropyl-isophthalamide, or

*N*-[1-(*S*)-(3,5-Difluoro-benzyl)-2-(*S*)-hydroxy-4-(*R*)-(prop-2-ynylcarbamoyl)-pentyl]-5-methy-*N,N*-dipropyl-isophthalamide.